

Coronary CT angiography: how should physicians use it wisely and when do physicians request it appropriately?

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Abstract

Coronary CT angiography has been increasingly used in the diagnosis of coronary artery disease due to rapid technological developments, which are reflected in the improved spatial and temporal resolution of the images. High diagnostic accuracy has been achieved with 64- and more slice CT scanners and in selected patients, coronary CT angiography is regarded as a reliable alternative to invasive coronary angiography. Although the tremendous contributions of coronary CT angiography to cardiac imaging are acknowledged, appropriate use of cardiac CT as the first line technique by physicians has not been well established. Optimal selection of cardiac CT is essential to ensure acquisition of valuable diagnostic information and avoid unnecessary invasive procedures. This is of paramount importance since cardiac CT not only involves patient risk assessment, prediction of major cardiac events, but also impacts physician decision-making on patient management. Applications of CT in cardiac imaging include coronary artery calcium scoring for predicting the patient risk of developing major cardiac events, followed by coronary CT angiography which is commonly used to determine the diagnostic and prognostic accuracy in the coronary artery disease. This review presents an overview of the applications of CT in cardiac imaging in terms of coronary calcium scoring and coronary CT angiography. Judicious use of both cardiac CT tools will be discussed with regard to their value in different patient risk groups with the aim of identifying the appropriate criteria for choosing a cardiac CT modality. An effective diagnostic pathway is finally recommended to physicians for appropriate selection of cardiac CT in clinical practice.

Keywords: coronary artery disease, coronary artery calcium, multislice CT, risk, radiation dose.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in developed countries. The diagnosis and management of CAD is increasingly dependent on non-invasive imaging modalities. Recent technological advances have led to a considerable increase in image quality for coronary imaging using multislice CT.¹⁻³ Numerous studies have shown that coronary CT angiography (CCTA), as a less-invasive alternative to coronary angiography, has a high diagnostic accuracy for the detection of significant CAD ($\geq 50\%$ lumen stenosis) when compared to invasive coronary angiography.³⁻⁹ High quality multislice CT (64-slice and higher) is not only able to provide reliable information on coronary luminal changes, but also has the potential to visualise coronary artery wall morphology, characterise atherosclerotic plaques and identify non-stenotic plaques that may be undetected by conventional coronary angiography. Studies have shown that CCTA demonstrates high prognostic value in CAD, as it is able to differentiate low-risk from high-risk patients¹⁰⁻¹², with very low rate of adverse cardiac events occurring in patients with normal CCTA, and significantly high rate of these events in patients with obstructive CAD.

It has been a regular procedure to perform both coronary artery calcium (CAC) scoring and CCTA for diagnosis in patients with suspected CAD. Results dealing with the incremental prognostic value of CAC scoring used in combination with CCTA have recently been published.¹³ Although satisfactory results have been achieved in these studies, with strengths and weaknesses being addressed, very few studies have specifically examined the clinical applications of CCTA in the particular target population, or risk stratification and assessment with regard to the judicious use of

CCTA.¹⁴⁻¹⁶ Identification of the exact role of CCTA in patients from different risk groups is clinically significant as this could lead to unnecessary examinations due to the fact that multislice CT is an imaging modality with high radiation dose. In addition, appropriate selection of CCTA is of paramount importance for physicians to choose CCTA as a gatekeeper for further diagnostic testing. This article explores how physicians should use multislice CT wisely in terms of the clinical value of coronary calcium scoring to predict the extent of coronary artery disease or cardiac events, and CCTA in patients from different risk groups with a focus on low to intermediate risk patients. The potential value and benefits of CCTA in asymptomatic patients are also explored. Finally, this article looks at when physicians should request CCTA appropriately from a clinical point of view by following the appropriate imaging pathways.

Current status of coronary CT angiography in coronary artery disease

With recent progress in the technical developments of multislice CT scanners, images can be acquired in a very short time with very high spatial resolution. In particular, the development of 64- or more slice CT scanners allows acquisition of cardiac images with a temporal resolution that is a fraction of the length of the cardiac cycle with an isotropic volume resolution of less than 0.5 mm.^{9, 17} Non-diagnostic CCTA studies have decreased from 15-25% with the early generation of 4- and 16-slice CT scanners to less than 10% with 64-slice CT scanners.^{17, 18} The cost of performing a CCTA examination is much lower than that of an invasive coronary angiography, and is equivalent to an imaging stress test. Unlike invasive coronary angiography, which is associated with procedure-related complications, CCTA is a less invasive modality with very rare

occurrence of complications resulting from CT examinations. Consequently, there has been extensive interest in the clinical application of CCTA in the evaluation of patients with suspected CAD.

Most studies have reported the diagnostic accuracy of CCTA by coronary artery segment, coronary artery and per patient assessment. Several meta-analyses of studies on the use of 64-slice CT reported mean sensitivities and specificities ranging from 85% to 99%, and 86% to 96%, respectively.^{3, 8, 19, 20} Given the dependence of positive predictive value and negative predictive value on the prevalence of disease, the relatively high prevalence of significant CAD as determined by invasive coronary angiography in many of these selected study populations compared to the general population raises a concern in appraising the value of CCTA in clinical practice. It has been shown that significant statistical heterogeneity exists among published studies, with smaller studies reporting higher diagnostic accuracy of CCTA in CAD.²¹ Two recent multicentre studies discussed several methodological limitations of CCTA, as patients with high calcium scores were excluded from the analysis of one study, while in another study, no segments were excluded from the analysis despite high calcium scores,^{4, 6} Therefore, reports of the diagnostic value of CCTA in CAD in the literature need to be interpreted with caution.

Coronary artery calcium scoring –predictive value in CAD

Quantifying the amount of coronary artery calcium with unenhanced CT calcium scoring has been widely accepted as a reliable non-invasive technique for screening risk of future cardiac events^{22, 23}, and is usually quantified by using the Agatston score or scores such as the volume score or calcium mass.²⁴⁻²⁶ Clinical application of CAC has been supported by evidence showing that absence of calcium reliably excludes obstructive

coronary artery stenoses ²⁷, and that the amount of CAC is a strong predictor for risk assessment of myocardial infarction and sudden cardiac death, independent of conventional coronary risk factors. ²⁸⁻³⁰ However, the prognostic value of CAC depends on the risk groups as to whether patient risk is reclassified and patient management can be changed based on CAC scores when compared to traditional risk assessments. ³¹ The Framingham risk score is one of the most commonly used risk-estimation systems, which enables clinicians to estimate cardiovascular risk in asymptomatic patients. It is calculated using traditional risk predictors, including age, gender, total cholesterol, high-density lipoprotein cholesterol, smoking status, and systolic blood pressure, and is represented as a 10-year risk score for the prediction of coronary heart disease events. ³² However, there is growing evidence to show that these traditional risk assessment methods, based on risk factor analysis, have significant limitations when used to guide individual patient therapy. ³²⁻³⁴ CAC score by multislice CT has been increasingly used as an additional assessment tool to evaluate the risk of developing major cardiac events in asymptomatic and symptomatic patients.

Coronary artery calcium scoring–predictive value in asymptomatic patients

In asymptomatic individuals, zero CAC is associated with a very low (<1% per year) risk of major cardiac events over the next 3-5 years, whereas in asymptomatic patients with extensive coronary calcification, the major cardiac events have been reported to be increased by up to 11-fold. ³⁵⁻³⁷ Several large population-based studies have reported that in asymptomatic patients without known CAD, CAC is predictive of future cardiac events above and beyond traditional risk factors ³⁸⁻⁴⁰. The recent population-based multi-ethnic study of atherosclerosis, conducted in 6,722 asymptomatic patients belonging to

four racial ethnic groups and followed for 3.8 years, showed a significant difference in the prevalence of CAC among different ethnic groups. Nonetheless, CAC has demonstrated incremental prognostic value over traditional risk factors, with a seven-fold increase in the incidence of cardiac events for Agatston scores >100 when compared with patients with zero CAC.³⁸

Other studies evaluating the prognostic value of the measurement of CAC have shown that coronary calcification is predictive of cardiac events in asymptomatic patients with different age groups.³⁹⁻⁴¹ LaMonte *et al.* in their study consisting of nearly 11,000 patients ranging from 22 to 96 years of age who underwent a screening medical examination, reported increased cardiac events in patients with coronary calcium scores of 400 or more during a mean follow-up of 3.5 years.⁴⁰ In the Prospective Army Coronary Calcium Project among men and women 40 to 45 years of age, Talyor *et al.* concluded that the presence of coronary calcium was associated with an increase in the risk of coronary events by a factor of 12 during 3 years of follow-up.³⁹ Similarly, higher calcium scores were found to be associated with the relative risks of coronary events in the population-based Rotterdam Study of elderly asymptomatic patients.⁴¹

Coronary calcium score—prognostic value in symptomatic patients

Coronary calcification is considered only marginally related to the degree of coronary stenosis and it is well known that both obstructive and non-obstructive CAD can occur in the absence of calcification.⁴²⁻⁴⁴ Significantly, coronary stenoses are frequently found to be non-calcified, and highly calcified plaques are frequently non-obstructive. Thus, the value of a zero or low calcium score (a low coronary calcium score is defined as an Agatston score of 1 to 100 because a coronary calcium score of 100 is often used as a cut-

off point for risk assessment) in symptomatic patients remains unclear. Several studies have reported the presence of obstructive non-calcified plaque in up to 8.7% of symptomatic patients with zero or low calcium score.⁴⁵⁻⁴⁷ The question has been raised as to whether only using CAC score is a reliable tool of determining the extent of CAD, since non-calcified coronary artery plaque may not be detected. Cheng *et al.* reported that low but detectable CAC scores are less reliable in predicting plaque burden due to their association with high overall non-calcified coronary artery plaque.⁴⁵ They concluded that low CAC scores are significantly less predictive of prevalence or severity of underlying non-calcified coronary plaque.

It has been recently suggested in some studies that coronary CT calcium score assessed with unenhanced CT may be supported by CCTA, or CCTA may be performed alone with the aim of acquiring more diagnostic information.⁴⁸⁻⁵⁰ CCTA allows not only visualisation of the vessel lumen, but also of the vessel wall, including composition of atherosclerotic plaque (calcified versus non-calcified or mixed type of plaques). However, the contrast enhancement in the coronary artery vessels may obscure detection of plaque, especially the presence of extensively calcified plaques, and thus may obviate reliable measurements of plaque density. CCTA was found to underestimate higher Agatston scores.⁴⁸ It has been reported in that study that CCTA allows for the detection of CAC with high accuracy, as well as good correlation with unenhanced CT calcium score. In contrast, in patients with zero or low calcium score, CCTA was found to provide additional valuable information on patient management as CCTA detected obstructive coronary lesions in 7% of patients with a zero score and in 17% with a low CAC score. Their study indicated that in symptomatic patients with a zero or low CAC

score on CT CAC scoring can be used to exclude an acute or long-term coronary syndrome, whereas CCTA is recommended as the non-invasive test of choice in these patients.⁴⁸ Similarly, van Werkhoven *et al.* in their recent report showed that CCTA provided additional prognostic information regarding stenosis severity and plaque composition when compared to CAC score for risk stratification in patients with suspected CAD. Their study involved analysis of plaque composition with CCTA, and results showed that the number of segments with non-calcified plaques and the number of segments with mixed plaques was found to be independently associated with increased risk for adverse cardiac events.⁵⁰

Coronary CT angiography in high-risk patients

The pre-test probability of CAD may have a significant impact on the diagnostic performance of the CT scan. Pre-test probability or likelihood is defined according to Diamond and Ferrester criteria, which are based on age, gender and symptomatic status.⁵¹ Intermediate likelihood is defined as a pre-test probability between 13.4% and 87.2%, while low and high pre-test probability are defined as less than 13.4% and more than 87.2%, respectively. It is noticed that the diagnostic performance of CCTA is different in patients from different risk groups. The diagnostic accuracy of CCTA has been extensively studied in populations with a high pre-test likelihood for CAD.¹⁷⁻²⁰ However, this population is unlikely to benefit from CCTA because most patients require invasive coronary angiography for the purpose of revascularisation. Meijboom *et al.* in their prospective study observed that, in patients with a high pre-test likelihood for CAD, interpretations using CCTA failed to significantly change the post-test probability of significant CAD. Thus, normal findings of CCTA did not result in a sufficient reduction

of the post-test probability to reliably rule out the presence of significant CAD. These data indicate that the majority of these symptomatic patients are likely to proceed to invasive coronary angiography despite the negative CCTA findings.¹⁵ CCTA is considered to be of limited clinical value in the evaluation of the high pre-test probability group. In patients with a high pre-test likelihood for significant stenosis, functional evaluation, such as myocardial perfusion imaging, may be more relevant than CCTA to determine the need for revascularisation.

Coronary CT angiography in low- and intermediate- risk patients

In contrast to the high pre-test probability group, patients with an intermediate or low pre-test likelihood for CAD might receive more benefit from CCTA. A very high negative predictive value (>99%) of CCTA reliably rules out the presence of significant CAD and can be used as a highly effective gatekeeper for invasive coronary angiography.^{14, 52, 53} Thus, when CCTA is used in a patient population with a low or intermediate pre-test likelihood, the need for additional imaging will be restricted to those patients with an abnormal finding from CCTA. Consequently, the use of CCTA could avoid invasive coronary angiography in most patients. This concept is also supported by relevant data about cost-effectiveness. Min *et al.* investigated the value of CCTA as a first line test compared to myocardial perfusion imaging using single photon emission computed tomography (SPECT) in patients with a low to intermediate pre-test likelihood. They concluded that lower referral rates to invasive coronary angiography and lower healthcare costs were observed in their low-risk group.⁵⁴

Diagnostic value of coronary CT angiography in the detection of atherosclerosis in low- to intermediate-risk groups has been confirmed in a latest study performed by 64-slice

CT compared to myocardial perfusion imaging. Iwasaki *et al.* in their study used 64-slice CT to detect subclinical atherosclerosis in 415 asymptomatic patients with more than 95% belonging to low- and intermediate-risk groups.⁵⁵ Their results showed very high prevalence (71%) of subclinical atherosclerosis in patients with low to intermediate risk patients, with one-fifth of them having significant coronary stenosis. This is supported by other studies showing the high prevalence of atherosclerosis. Hausleiter *et al.*⁴⁶ reported the prevalence of coronary plaques was 67.1%, in their study comprising of 161 patients with an intermediate risk for coronary artery disease. Choi *et al.* studied 1000 middle-aged asymptomatic patients with 64-slice CT and noticed the prevalence of 22% atherosclerotic plaques in these patients.⁵⁶ These studies further testified that coronary CT angiography is a valuable imaging modality for detection of atherosclerotic changes in the low- to intermediate-risk patients.

Coronary CT angiography in asymptomatic patients

Despite the high diagnostic accuracy of coronary artery stenosis and prognostic power of CCTA in symptomatic patients, to date there have been very limited publications evaluating the prognostic potential of CCTA in asymptomatic patients. Although only limited data are available in asymptomatic patient populations, it is possible that CCTA is valuable for risk stratification in these patients, since CCTA can be used to detect atherosclerosis for long-term risk assessment.⁵⁷⁻⁵⁹ The prevalence of atherosclerosis was reported to be 22% in a recent study consisting of 1,000 asymptomatic individuals undergoing CCTA, with 5% and 2% being observed in $\geq 50\%$ CAD and $\geq 75\%$ CAD, respectively.⁵⁷ Cardiac events occurred in 1.5% of individuals during a follow-up of 17 months, all of whom had atherosclerosis on CCTA. These data indicate that CCTA is

currently not acceptable as a general screening tool and CAC score testing may be a preferable option. However, non-invasive CCTA may potentially be used as a test in the workup of asymptomatic individuals with cardiac risk characteristics.⁵⁷⁻⁶⁰

It has been recently reported that performing CCTA before invasive coronary angiography is a cost-effective strategy in the management of patients without symptoms who have positive stress test results.⁵⁹ It is generally believed that a patient at low risk who has a positive stress test result (such as treadmill ECG studies, stress echocardiography, and radionuclide stress studies) is often referred for cardiac catheterisation, especially when the positive stress test result is obtained in a preoperative workup. Halpern *et al.* in their study using decision tree analysis reported that when a patient with an expected CAD prevalence of less than 85% is found to have a positive test result, CCTA is a less expensive alternative to invasive coronary angiography.⁵⁹ Although most patients undergo screening for CAD with stress tests to obtain functional and perfusion information which is not available with CCTA, a meta-analysis on more than 35,000 patients with coronary angiography as the reference standard showed that only average sensitivity and specificity was achieved with stress echocardiography and SPECT.⁶¹ Thus, the use of CCTA in asymptomatic patients can avoid unnecessary invasive cardiac angiography procedures.

Coronary CT angiography–radiation dose issue

Radiation exposure associated with coronary CT angiography has increased substantially over the past two decades and it is a major concern that needs to draw attention of both clinicians and manufacturers. The general view about radiation dose is that coronary CT angiography is associated with a risk of cancer development. The recent Biological

Effects of Ionising Radiation (BEIR) VII provides a framework for estimating cancer risk associated with radiation exposure from ionising radiation.⁶² According to the report, it is estimated that 1 in 1000 people will develop cancer due to an exposure of 10 mSv. Brenner and Hall⁶³ estimated that approximately 1.5% to 2% of all cancers in the United States may be caused by radiation exposure from CT examinations. Davies *et al* estimated that in the UK radiation from CT scans causes 800 cancers a year in women and 1300 in men.⁶⁴ Radiation exposure is especially important for young and female patients who present with atypical symptoms, but do not have high pre-test likelihood for having haemodynamically significant coronary stenosis. A recent study reported that one in 270 women aged 40 years who undergo coronary CT angiography will develop cancer.

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The number of CT scans is being increased significantly in Australia. According to 2008-09 Annual Report of the CEO of ARPANSA that the number of CT examinations in Australia increased greatly from 1994 (612,438 cases) to 2008 (1,935,802 cases) which is more than a 3-fold increase.⁶⁶ Coronary CT angiography should be performed with dose-saving strategies whenever possible to reduce the radiation dose to patients. The reader is referred to several excellent review articles on dose reduction strategies currently recommended in coronary CT angiography.^{9, 67-69} Judicious use of multislice CT in cardiac imaging by clinicians is essential to maximise its clinical applications while minimising the potential risk of radiation exposure.

The basic principle of radiation protection is to keep radiation exposure “as low as reasonably achievable” (the ALARA principle). Thus, if CAC scoring has no added benefit over CCTA in the routinely combined CAC scoring and CCTA scans, CAC

scoring may not be necessarily incorporated into the CCTA protocol. Kwon *et al.* in their recent prospective study concluded that CCTA has positive correlation with CAC scores for prediction of major adverse cardiac events, and CCTA has better predictive value than CAC scoring in low-risk patients suspected of CAD.⁷⁰ Their results showed no added benefit to the addition of CAC scoring to CCTA, although their study population was restricted to a relatively low-risk group. Further studies based on multicentres with inclusion of large sample size are required to confirm their initial results.

Summary and Conclusion

The introduction of CCTA has significantly changed the clinical diagnostic approach to CAD. There is no doubt that, in patients with clinical suspected CAD, CCTA plays a significant role in establishing or excluding the diagnosis. With a very high negative predictive value, CCTA is widely regarded as a reliable technique in clinical practice to exclude significant CAD.

Use of CCTA for diagnosis and risk assessment in patients with low or intermediate risk or pretest probability for coronary artery disease is favourably preferred, whereas in high-risk patients, CCTA is less favourably recommended. Use of non-contrast CT for coronary artery calcium scoring is considered an appropriate approach in low- and intermediate-risk patients for prediction of cardiac events, while in symptomatic or high-risk patients, its predictive value is less reliable due to high prevalence of non-calcified plaques. Appropriate selections of cardiac CT will have a significant impact on physician decision-making and performance that will guide appropriate patient management strategies. The flow chart (Figure 1) recommends the CT imaging pathways for physicians to choose multislice CT appropriately in patients with suspected coronary

artery disease and within different pre-test probabilities or risk groups. It is expected that it will assist physicians, particularly cardiologists, to make judicious use of cardiac CT in their clinical practice.

References

1. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of non-invasive coronary angiography using 64-slice spiral computed tomography. *J Am Coll Cardiol* 2005, 46: 552-557.
2. Wintersperger BJ, Nikolaou K, von Ziegler F, et al. Image quality, motion artifacts, and reconstruction timing of 64-slice coronary computed tomography angiography with 0.33-second rotation speed. *Invest Radiol* 2006;41: 436–442.
3. Sun Z, Lin CH, Davidson R, et al. Diagnostic value of 64-slice CT angiography in coronary artery disease: A systematic review. *Eur J Radiol* 2008; 67: 78-84.
4. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008; 359: 2324-2326.
5. Schuijf JD, Pundziute G, Jukema JW, et al. Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease. *Am J Cardiol* 2006;98:145–148.
6. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724-1732.
7. Meijboom WB, Meijs MFL, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective multicenter, multivendor study. *J Am Coll Cardiol* 2008;52:2135-2144.

8. Abdulla J, Abildstrom SZ, Gotzsche O, et al. 64-Multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: a systematic review and meta-analysis. *Eur Heart J* 2007;28:3042–3050.
9. Sun Z, GH Choo, Ng KH. Coronary CT angiography: current status and continuing challenges. *Br J Radiol* 2011 (in press).
10. Carrigan TP, Nair D, Schoenhagen P, et al. Prognostic utility of 64-slice computed tomography in patients with suspected but no documented coronary artery disease. *Eur Heart J* 2009; 30:362-371.
11. Min JK, Feignouz J, Treutenaere J, et al. The prognostic value of multidetector coronary CT angiography for the prediction of major adverse cardiac events: a major multicenter observational cohort study. *Int J Cardiovasc Imaging* 2010 (Epub ahead of print) DOI 10.1007/s10554-010-9613-4.
12. Abdulla J, Asferg C, Kofoed KF. Prognostic value of absence or presence of coronary artery disease determined by 64-slice computed tomography coronary angiography: a systematic review and meta-analysis. *Int J Cardiovasc Imaging* 2010 (Epub ahead of print). DOI 10.1007/s10554-010-9666-4.
13. Ostrom MP, Gopal A, Ahmadi N, et al. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. *J Am Coll Cardiol* 2008; 52: 1335-1343.
14. van Werkhoven JM, Gaemperli O, Schuijf JD, et al. Multislice computed tomography coronary angiography for risk stratification in patients with an intermediate pretest likelihood. *Heart* 2009; 95: 1607-1611.

15. Meijboom WB, Van Mieghem CA, Mollet NR, et al. 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. *J Am Coll Cardiol* 2007;50:1469–1475.
16. Henneman MM, Schuijf JD, van Werkhoven JM, et al. Multi-slice computed tomography coronary angiography for ruling out suspected coronary artery disease: what is the prevalence of a normal study in a general clinical population? *Eur Heart J* 2008;29:2006–2013.
17. Nasis A, Leung MC, Antonis PR, et al. Diagnostic accuracy of non-invasive coronary angiography with 320-detector row computed tomography. *Am J Cardiol* 2010; 106: 1429-1435.
18. Sun Z, Jiang W. Diagnostic value of multislice CT angiography in coronary artery disease: A meta-analysis. *Eur J Radiol* 2006; 60: 279-286.
19. Vanhoenacker PK, Heijenbroek-Kal MH, Van Heste R, Decramer I, Van Hoe LR, Wijns W, et al. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. *Radiology* 2007; 244: 419-428.
20. Mowatt G, Cook JA, Hillis GS, et al. 64-slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. *Heart* 2008; 94: 1386–1393.
21. Hamon M, Biondi-Zoccai GG, Malagutti P, et al. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. *J Am Coll Cardiol* 2006; 48:1896-1910.

22. Oudkerk M, Stillman AE, Halliburton SS, et al. Coronary artery calcium screening: current status and recommendations from the European Society of Cardiac Radiology and North American Society for Cardiovascular Imaging. *Int J Cardiovasc Imaging* 2008; 24:645–671.
23. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *Circulation* 2007; 115:402–426.
24. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15:827–832.
25. Callister TQ, Coil B, Raya SP, et al. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology* 1998; 208:807–814.
26. Hoffmann U, Siebert U, Bull-Stewart A, et al. Evidence for lower variability of coronary artery calcium mineral mass measurements by multidetector computed tomography in a community based cohort—consequences for progression studies. *Eur J Radiol* 2006; 57:396–402.
27. Haberl R, Becker A, Leber A, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol* 2001;37:451– 457.

28. Keelan PC, Bielak LF, Ashai K, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation* 2001; 104:412–417.
29. Wong ND, Hsu JC, Detrano RC, et al. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000; 86:495–498.
30. Arad Y, Spadaro LA, Goodman K, et al. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000; 36:1253–1260.
31. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3142
32. Johnson KM, Dowe DA, Brink JA. Traditional clinical risk assessment tools do not accurately predict coronary atherosclerotic plaque burden: a CT angiography study. *AJR Am J Roentgenol* 2009;192:235-243.
33. Akosah KO, Schaper A, Cogbill C, et al. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? *J Am Coll Cardiol* 2003;41:1475-1479.
34. Nasir K, Michos ED, Blumenthal RS, et al. Detection of high-risk young adults and women by coronary calcium and National Cholesterol Education Program Panel III guidelines. *J Am Coll Cardiol* 2005;46: 1931-1936.

35. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/ AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2007;49:378–402.
36. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;358:1336–1345.
37. Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. *JACC Cardiovasc Imaging* 2009;2: 675–688.
38. Budoff MJ, Nasir K, McClelland RL, et al. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2009;53:345–352.
39. Taylor AJ, Bindeman J, Feuerstein I, et al. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. *J Am Coll Cardiol* 2005;46:807–814.
40. LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. *Am J Epidemiol* 2005;162:421-429.

41. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation* 2005;112:572-577.
42. Gottlieb I, Miller JM, Arbab-Zadeh A, et al.: The absence of coronary calcification does not exclude obstructive coronary artery disease or the need for revascularization in patients referred for conventional coronary angiography. *JAmColl Cardiol* 2010, 55:627–634.
43. Chang SM, Nabi F, Xu J, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. *J Am Coll Cardiol* 2009, 54:1872–1882.
44. Lau GT, Ridley LJ, Schieb MC, et al. Coronary artery stenoses: detection with calcium scoring, CT angiography, and both methods combined. *Radiology* 2005, 235:415–422.
45. Cheng VY, Lepor NE, Madyoon H, et al. Presence and severity of noncalcified coronary plaque on 64-slice computed tomographic coronary angiography in patients with zero and low coronary artery calcium. *Am J Cardiol* 2007; 99:1183–1186.
46. Hausleiter J, Meyer T, Hadamitzky M, et al. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol* 2006; 48: 312-318.
47. Akram K, O'Donnell RE, King S, et al. Influence of symptomatic status on the prevalence of obstructive coronary artery disease in patients with zero calcium score. *Atherosclerosis* 2009; 203: 533-537.
48. Rubinshtein R, Gaspar T, Halon DA, et al. Prevalence and extent of obstructive coronary artery disease in patients with zero or low calcium score undergoing 64-slice

cardiac multidetector computed tomography for evaluation of a chest pain syndrome. *Am J Cardiol* 2007; 99:472–475.

49. van der Bijl N, Joemai RMS, Geleijns J, et al. Assessment of Agatston coronary artery calcium score using contrast-enhanced CT coronary angiography. *AJR Am J Roentgen* 2010; 195: 1299-1305.
50. van Werkhoven, Shuijf JD, Gaemperli O, et al. Incremental prognostic value of multislice computed tomography coronary angiography over coronary artery calcium scoring in patients with suspected coronary artery disease. *Eur Heart J* 2009; 30: 2622-2629.
51. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;300:1350–1358.
52. Leber AW, Johnson T, Becker A, et al. Diagnostic accuracy of dual-source multislice CT-coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. *Eur Heart J* 2007;28:2354 –2360.
53. van Werkhoven JM, Heijenbrok MW, Schuijf JD, et al. Diagnostic accuracy of 64-slice multislice computed tomographic coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. *Am J Cardiol* 2010; 105: 302-305.
54. Min JK, Kang N, Shaw LJ, et al. Costs and clinical outcomes after coronary multidetector CT angiography in patients without known coronary artery disease: comparison to myocardial perfusion SPECT. *Radiology* 2008;249:62–70.

55. Iwasaki K, Matsumoto T, Aono H, et al. Prevalence of subclinical atherosclerosis in asymptomatic patients with low-to-intermediate risk by 64-slice computed tomography. *Coron Artery Dis* 2010; 22: 18-25.
56. Choi EK, Choi SI, Rivera JJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. *J Am Coll Cardiol* 2008;52:357-365.
57. Hadamitzky M, Meyer T, Hein F, et al. Prognostic value of coronary computed tomographic angiography in asymptomatic patients. *Am J Cardiol* 2010; 105: 1746 – 1751.
58. van Werkhoven JM, Bax JJ, Nucifora G, et al. The value of multi-slice-computed tomography coronary angiography for risk stratification. *J Nucl Cardiol* 2009; 16: 970-980.
59. Halpern EJ, Savage MP, Fischman DL, Levin DC. Cost-effectiveness of coronary CT angiography in evaluation of patients without symptoms who have positive stress test results. *AJR Am J Roentgen* 2010; 194: 1257-1262.
60. Hwang Y, Kim Y, Chung IM, et al. Coronary heart disease risk assessment and characterization of coronary artery disease using coronary CT angiography: comparison of asymptomatic and symptomatic groups. *Clin Radiol* 2010; 65: 601-608.
61. Heijenbroek-Kal MH, Fleischmann KE, Hunink MG. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. *Am Heart J* 2007; 154:415–423

62. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation; Nuclear and Radiation Studies Board, Division on Earth and Life Studies, National Research Council of the National Academies. Health Risks From Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. Washington, DC: The National Academies Press; 2006.
63. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007; 357(22):2277–2284.
64. Davies HE, Wathen CG, Gleeson FV. Risks of exposure to radiological imaging and how to minimise them. *BMJ* 2011; 342: 589-593.
65. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009; 169: 2078-2086.
66. Radiation Protection and Nuclear Safety Agency (ARPANSA), 2008-09 Annual Report of the CEO of ARPANSA, (ARPANSA, Melbourne, 2009).
67. Paul JF, Abada HT. Strategies for reduction of radiation dose in cardiac multislice CT. *Eur Radiol* 2007; 17:2028-2037.
68. Hausleiter J, Meyer T, Hermann F et al. Estimated radiation dose associated with cardiac CT angiography. *JAMA* 2009; 301(5):500–507.
69. Sun Z, Ng KH. Multislice CT angiography in cardiac imaging. Part III: radiation risk and dose reduction. *Singapore Med J* 2010; 51: 374-380.
70. Kwon SW, Kim YJ, Shim J, et al. Coronary artery calcium scoring does not add prognostic value to standard 64-section CT angiography protocol in low-risk patients suspected of having coronary artery disease. *Radiology* 2011 (Epub ahead of print).

Figure legend

Figure 1. Flow chart shows the imaging pathways for appropriate selection of multislice CT in patients with suspected CAD. CAD-coronary artery disease, CCTA-coronary CT angiography, CAC-coronary artery calcium, MI-myocardial infarction.

